Updates in the Management of GI Malignancies

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ROSWELL PARK
COMPREHENSIVE CANCER CENTER

The National Pancreas Foundation

Disclosures

- No disclosures

Outline

- Esophagogastric Cancer
- Pancreatic Cancer
- Hepatocellular Carcinoma and Cholangiocarcinoma
- Colorectal Cancer
- Neuroendocrine Tumors

Immuno-oncology, biomarkers and beyond

ESOPHAGOGASTRIC CANCER

Pembrolizumab Versus Chemotherapy as Second-line Therapy for Advanced Esophageal Cancer: The Phase 3 KEYNOTE-181 Study

Takashi Kojima,[1] Kei Muro,[2] Eric Francois,[3] Chih-Hung Hsu,[4] Toshikazu Moriwaki,[5] Sung-Bae Kim,[6] Se-Hoon Lee,[7] Jaafar Bennouna,[8] Ken Kato,[9] Lin Shen,[10] Shu-Qui Qin,[11] Paula Ferreira,[12] Toshihiko Doi,[13] Antoine Adenis,[14] Peter Enzinger,[15] Manish Shah,[16] Ruixue Wang,[17] Pooja Bhagia,[17] S. Peter Kang,[17] Jean-Philippe Metges[18]

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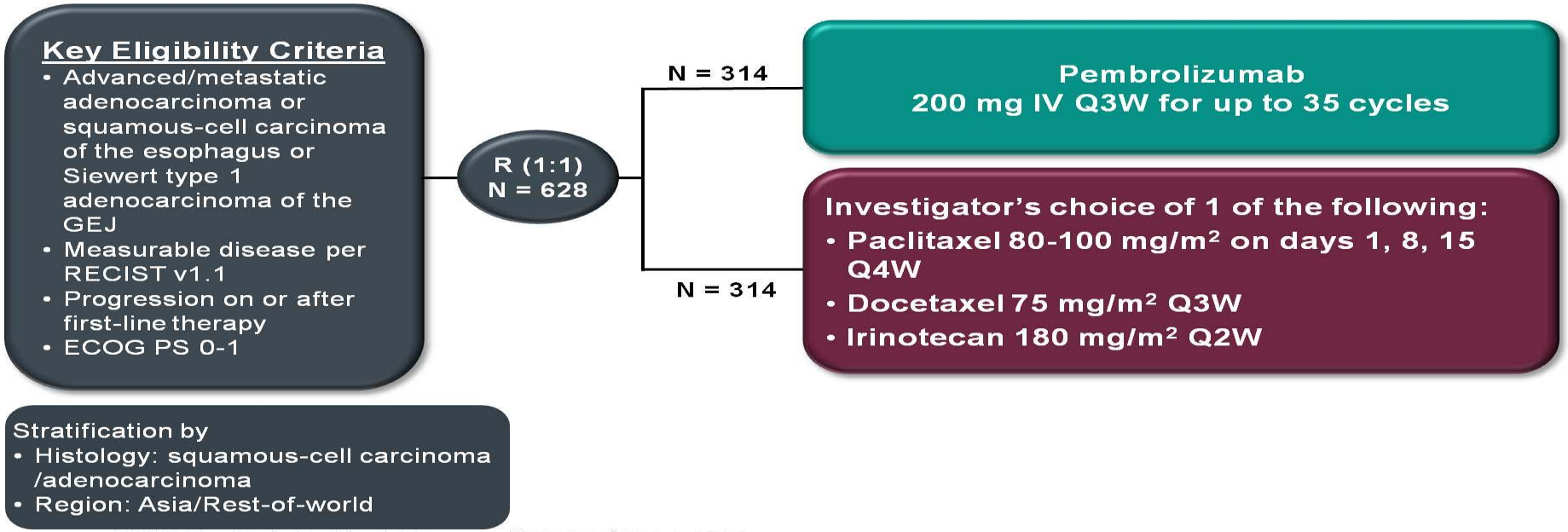
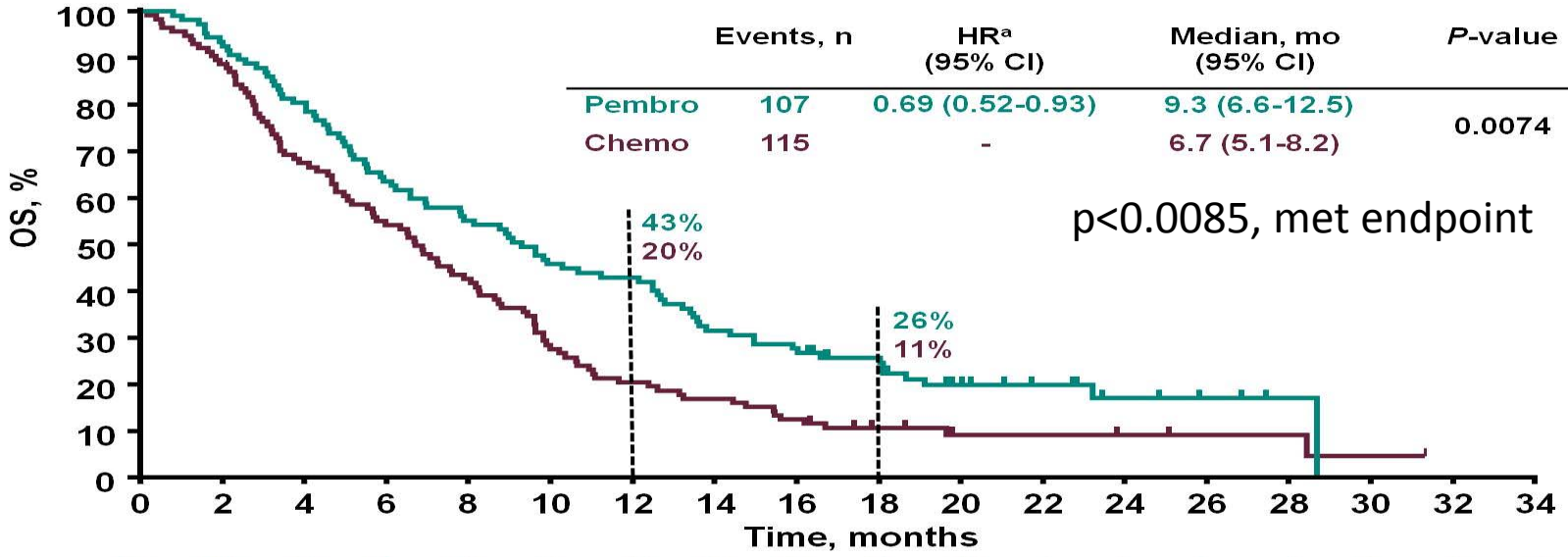
PRESENTED AT: 2019 Gastrointestinal Cancers Symposium | #GI19

Phase 3 KEYNOTE-181 Study (NCT02564263)



Overall Survival (PD-L1 CPS ≥10)



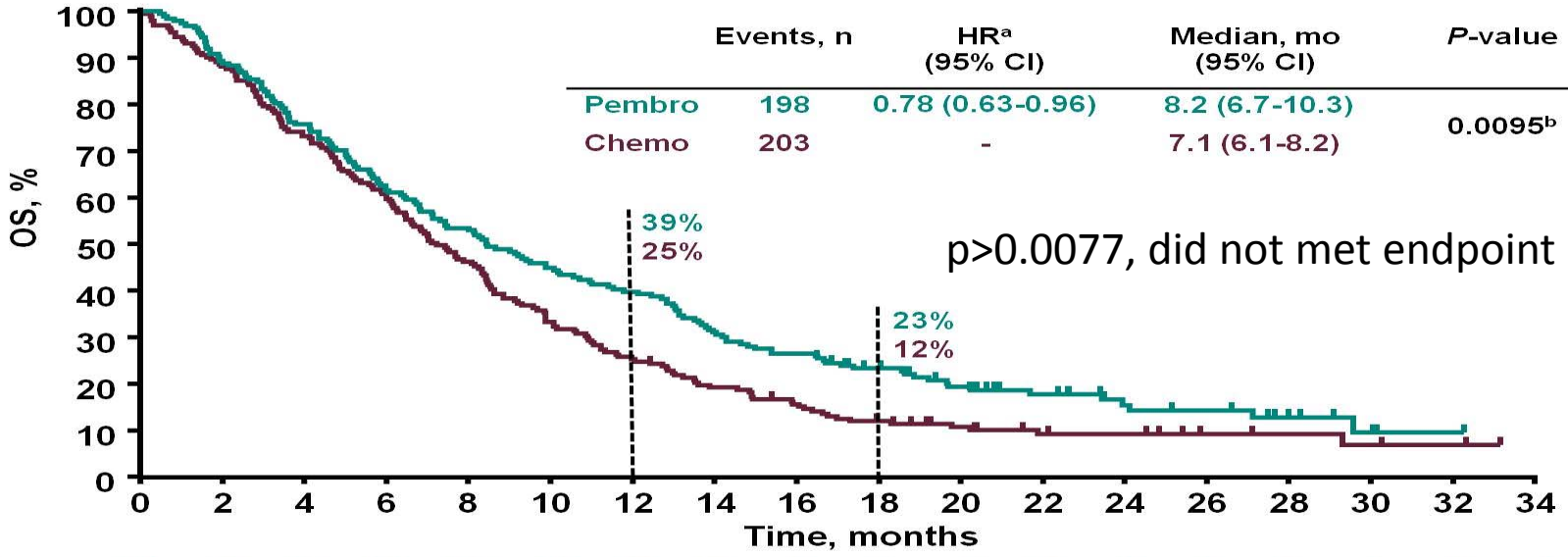
	Events, n	HR[a] (95% CI)	Median, mo (95% CI)	*P*-value
Pembro	107	0.69 (0.52-0.93)	9.3 (6.6-12.5)	0.0074
Chemo	115	-	6.7 (5.1-8.2)	

p<0.0085, met endpoint

No. at risk																		
Pembrolizumab	107	100	86	68	59	49	45	33	29	23	13	9	5	3	1	0	0	0
Chemotherapy	115	102	76	61	48	31	23	19	14	8	4	4	3	2	2	1	0	0

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology.
Data cutoff: October 15, 2018.

Overall Survival (SCC)



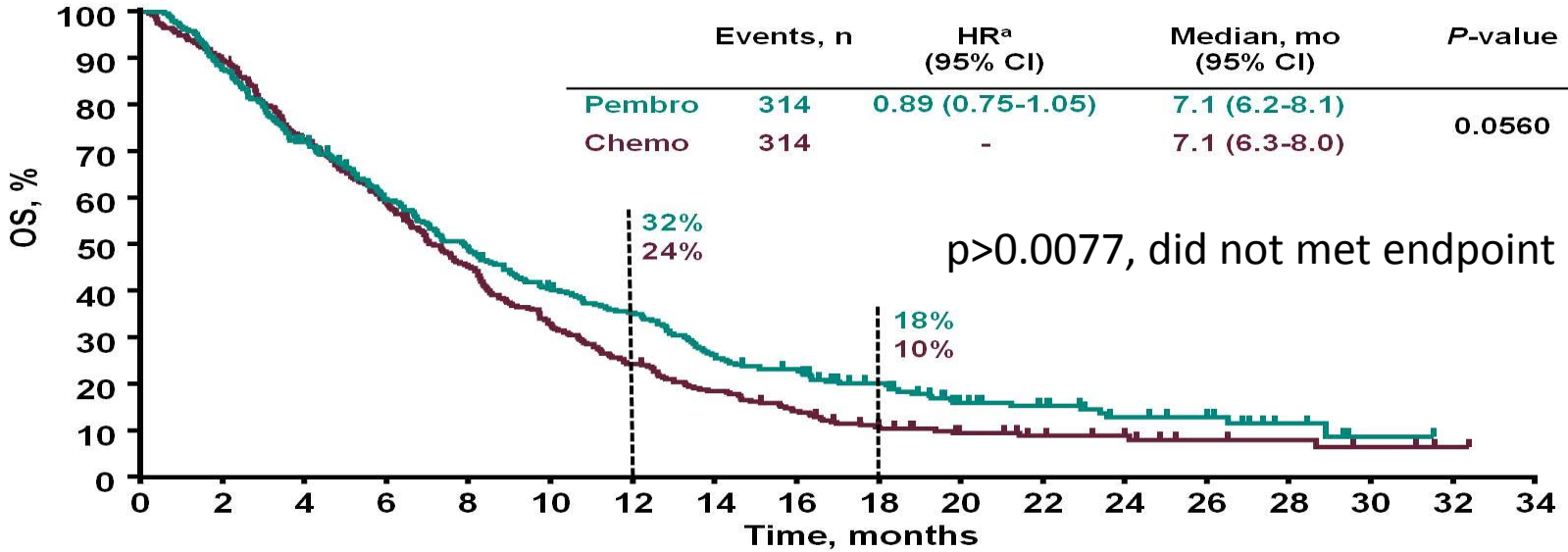
	Events, n	HR[a] (95% CI)	Median, mo (95% CI)	*P*-value
Pembro	198	0.78 (0.63-0.96)	8.2 (6.7-10.3)	0.0095[b]
Chemo	203	-	7.1 (6.1-8.2)	

p>0.0077, did not met endpoint

No. at risk																		
Pembrolizumab	198	177	150	121	103	86	77	57	52	38	24	17	12	10	5	1	0	0
Chemotherapy	203	179	147	118	91	64	50	38	27	20	13	10	8	5	4	2	1	0

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology; [b]Not significant based on pre-specified statistical boundaries of $P \leq 0.0077$ for superiority of OS in SCC; Data cutoff: October 15, 2018.

Overall Survival (ITT)



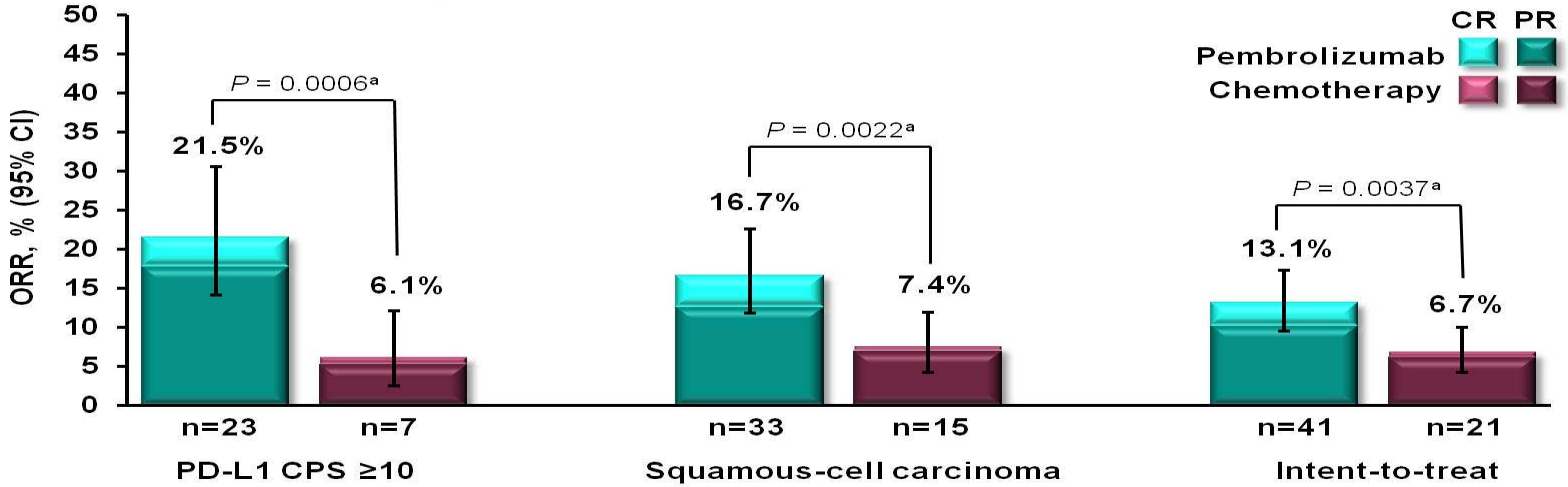
	Events, n	HR[a] (95% CI)	Median, mo (95% CI)	*P*-value
Pembro	314	0.89 (0.75-1.05)	7.1 (6.2-8.1)	0.0560
Chemo	314	-	7.1 (6.3-8.0)	

p>0.0077, did not met endpoint

No. at risk																		
Pembrolizumab	314	275	224	176	143	116	100	73	63	46	28	20	14	10	5	1	0	0
Chemotherapy	314	280	226	181	139	98	75	56	41	26	18	13	9	6	5	3	1	0

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology.
Data cutoff: October 15, 2018.

Response Rate and Duration
(RECIST v1.1, BICR)



Duration	Median, mo (range)	≥ 6 mo, %
Pembro	9.3 (2.1+ to 22.6+)	77
Chemo	7.7 (4.3 to 16.8+)	57

Duration	Median, mo (range)	≥ 6 mo, %
Pembro	8.5 (2.1+ to 25.8+)	68
Chemo	10.7 (2.1+ to 16.8+)	75

Duration	Median, mo (range)	≥ 6 mo, %
Pembro	8.5 (2.1+ to 25.8+)	72
Chemo	10.7 (1.8+ to 16.8+)	62

[a]Nominal; one-sided.
Data cutoff: October 15, 2018.

Pembrolizumab With or Without Chemotherapy Versus Chemotherapy in Advanced G/GEJ Adenocarcinoma: The Phase 3, KEYNOTE-062 Study

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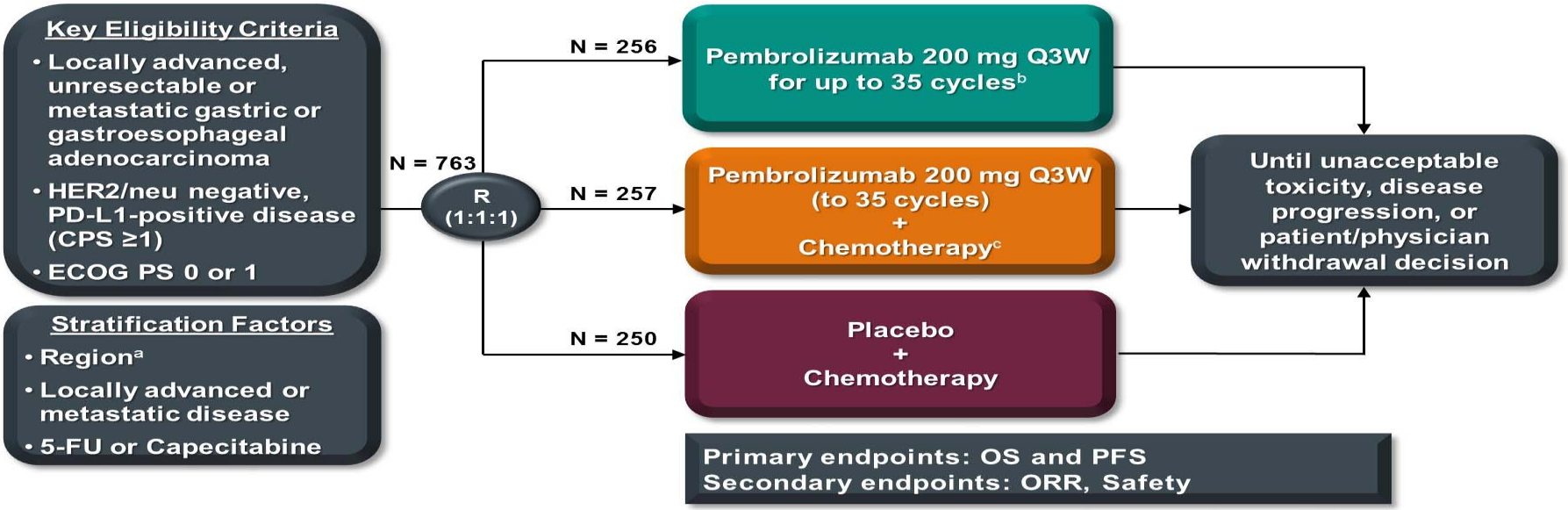
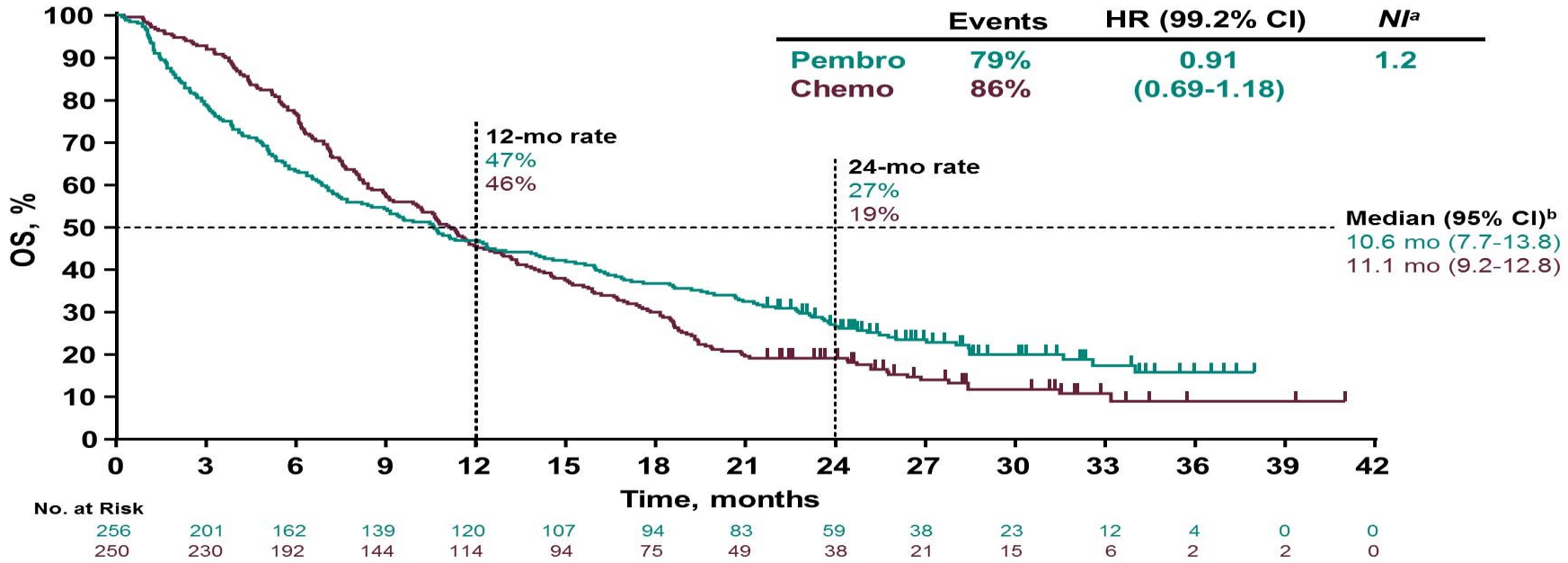
PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

KEYNOTE-062 Study Design (NCT02494583)



[a]EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
[b]Administration of pembrolizumab monotherapy was not blinded.
[c]Chemotherapy: Cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles as per country guidelines).

Overall Survival: P vs C (CPS ≥1)

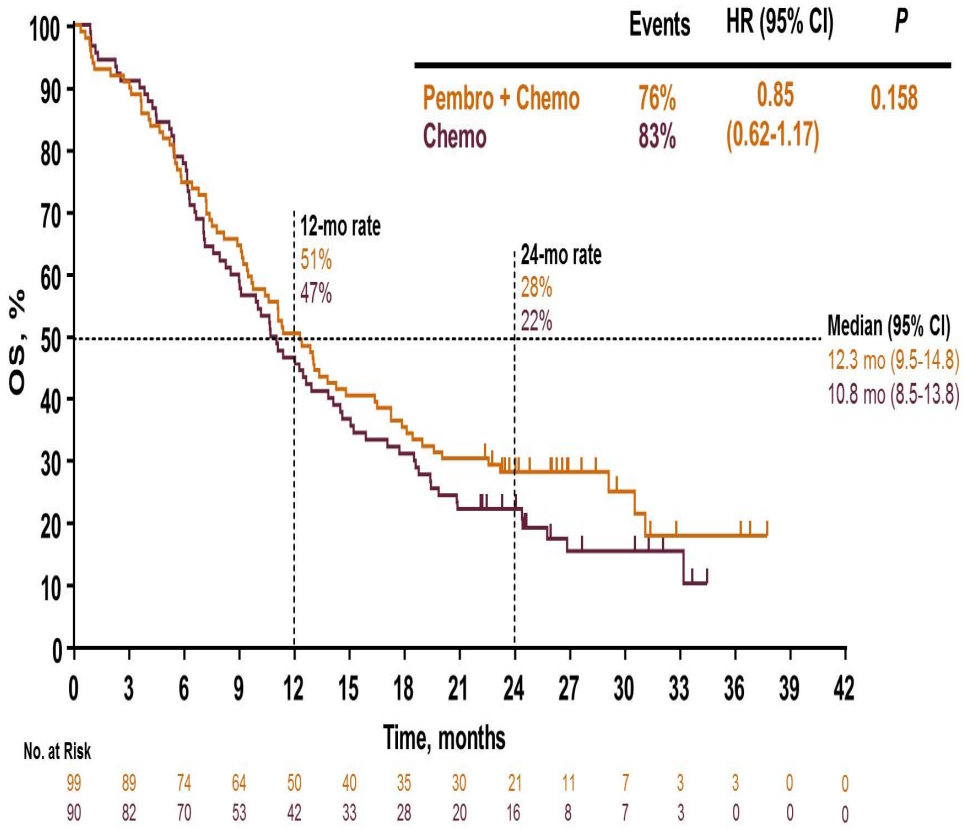


[a]NI, non-inferiority margin; [b]HR (95% CI) = 0.91 (0.74-1.10), *P* = 0.162 for superiority of P vs C; Data cutoff: March 26, 2019.

Pembrolizumab is non-inferior to chemo but the upper limit of CI is close

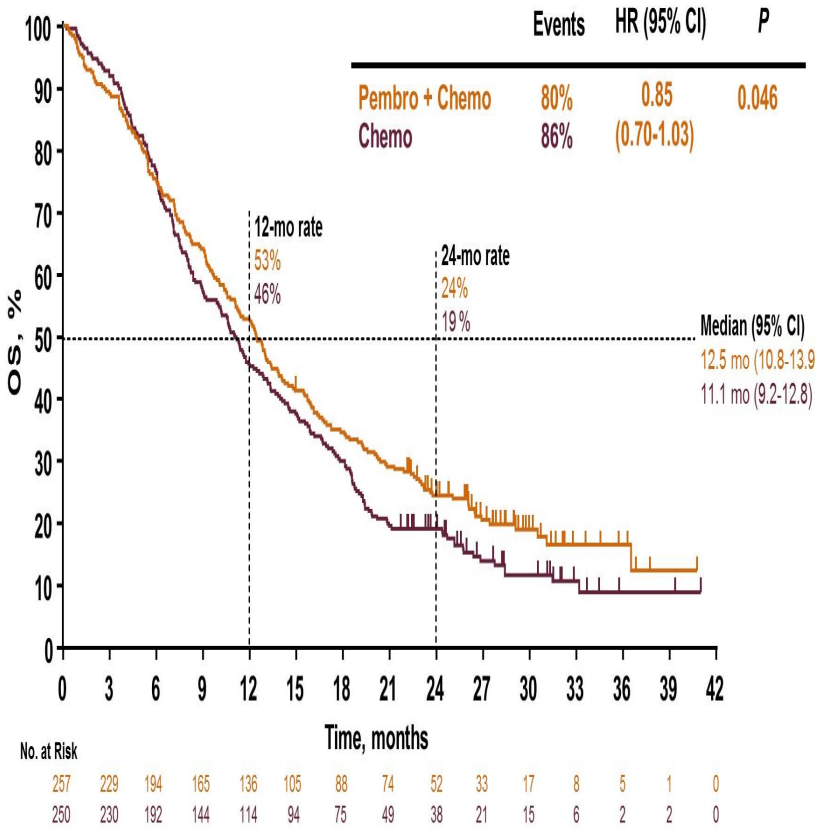
No superiority of chemo-immunotherapy for both CPS>10 and CPS>1

Overall Survival: P+C vs C (CPS ≥10)



Data cutoff: March 26, 2019.

Overall Survival: P+C vs C (CPS ≥1)



Data cutoff: March 26, 2019.

Old and new biomarkers

HER2 + (Janjigian ASCO GI 2019)

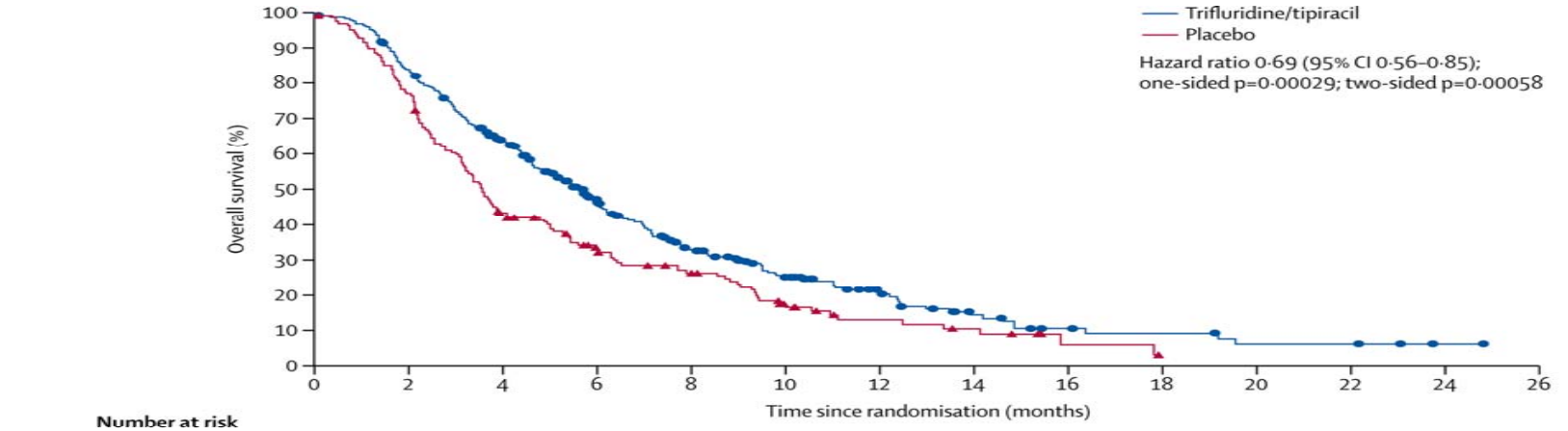
- Treatment-naïve, advanced disease
- HER2+/PDL1 any
- Trastuzumab+Pembrolizumab +CapeOx
- ORR: 83%, median PFS: 11.4 months

Claudin + (Sahin, ASCO GI 2019)

- FAST trial
- EOX vs. EOX plus zolbetuximab
  - OS ITT (Claudin +2>40%): 8.4 vs. 13 mo (HR 0.56)
  - Claudin +2 >70%: 8.9 vs 16.5 mo (HR 0.51)
- Ongoing Phase 3, Claudin >75%

TAGS study

- Advanced disease
- Trifluridine/Tipiracil vs. Placebo (2:1)
- At least 2 lines of prior therapy



The Lancet Oncology 2018 19, 1437-1448DOI: (10.1016/S1470-2045(18)30739-3)

Esophagogastric Cancer 2019

- Esophageal
  - Pembrolizumab 2nd line, SCCA/CPS>10
  - Keynote 590 (chemo+pembrolizumab vs. chemo) in progress
  - HER2: Keynote 811 (SOC vs SOC plus trastuzumab) in progress
  - Claudin 18.2: Spotlight (SOC vs SOC plus zolbetuximab) in progress
- Gastric
  - Pembrolizumab: 3rd line if CPS>1
  - Trifluridine/Tipiracil: 3rd line
  - HER2: Keynote 811 in progress
  - Claudin 18.2: Spotlight in progress

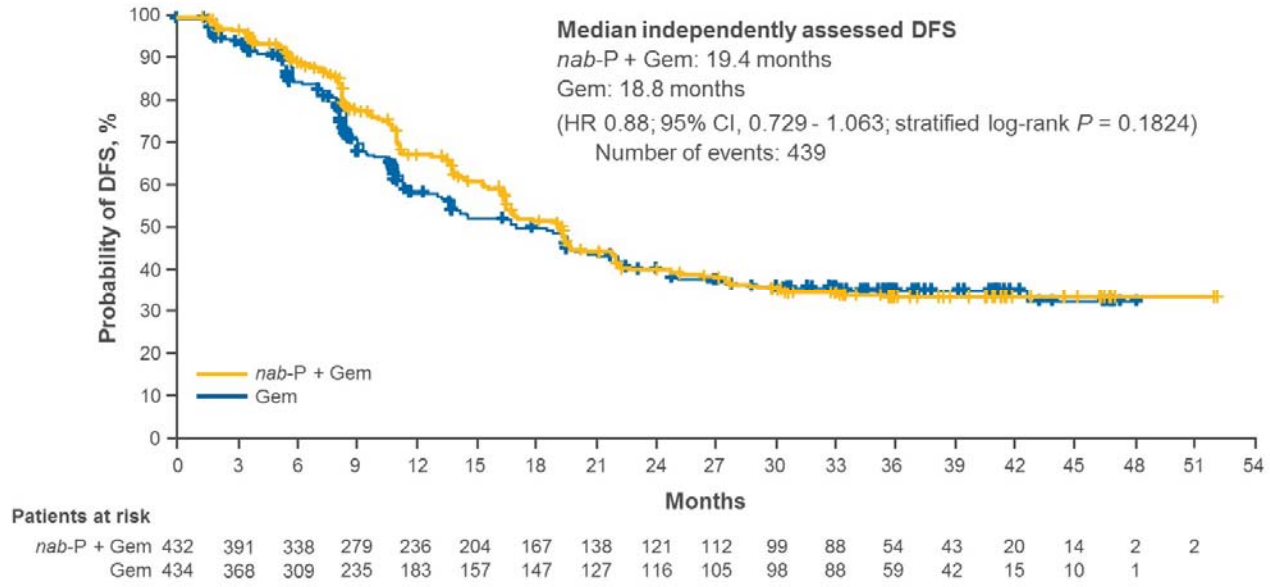
Localized and Advanced Disease Updates; Precision Medicine

PANCREATIC CANCER

APACT

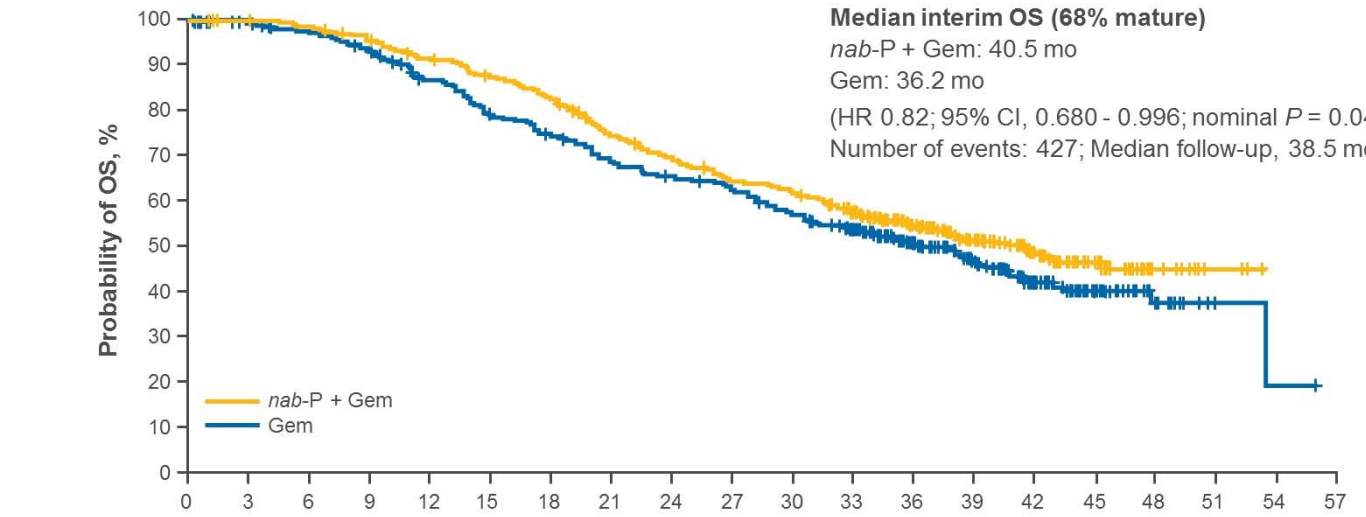
- Gemcitabine/Nab Paclitaxel plus Gemcitabine
- N=866
- R1 allowed (25% R1)
- CA19.9<100
- Up to 12 weeks from surgery

PRIMARY ENDPOINT: INDEPENDENTLY ASSESSED DFS (ITT POPULATION)



Presented by Margaret Tempero, MD, at ASCO 2019; abstract 4000: Adjuvant *nab*-Paclitaxel Plus Gemcitabine vs Gemcitabine

SECONDARY ENDPOINT: INTERIM OS (ITT POPULATION)



Median interim OS (68% mature)
nab-P + Gem: 40.5 mo
Gem: 36.2 mo
(HR 0.82; 95% CI, 0.680 - 0.996; nominal *P* = 0.045)
Number of events: 427; Median follow-up, 38.5 months

Patients at risk

nab-P + Gem	432	427	420	406	385	366	344	307	284	264	252	219	162	113	73	40	12	3
Gem	434	415	404	384	354	320	301	275	262	249	228	198	153	101	64	29	12	2	1

Presented by Margaret Tempero, MD, at ASCO 2019; abstract 4000: Adjuvant *nab*-Paclitaxel Plus Gemcitabine vs Gemcitabine

Adjuvant Treatment for Pancreatic Adenocarcinoma in 2019

Strategy	Overall Survival (months)
Observation	20.2 (CONKO-001)
Single-agent	22.8 (CONKO-001)/23.2 (ESPAC-3)/25.5 (ESPAC-4)/35 (PRODIGE 24)
Multi-agent	28 (ESPAC-4)/40 (APACT)/54.4 (PRODIGE 24)

* ESPAC-4 HR: 0.82 vs. APACT HR: 0.82 vs. PRODIGE 24 HR: 0.64
* ESPAC-4 OS ~40 months with gemcitabine/capecitabine and R0 resection

DNA Damage Response (DDR) Mutations in Pancreatic Cancer

- **17 – 25% of pancreatic adenocarcinomas harbor mutations in the DDR genes**
  - **Homologous recombination** DNA damage response (HR-DDR) mutations
  - *BRCA1, BRCA2, ATM, PALB2, ATRX, RAD51*, and others

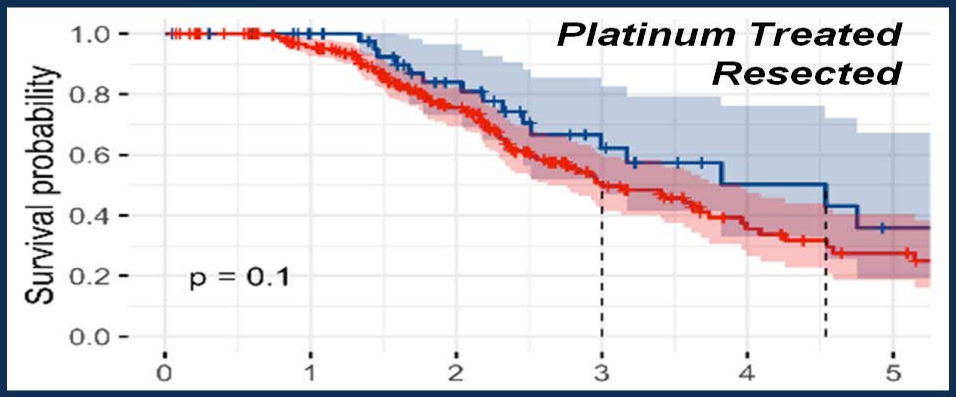
Gene	N (616 Total)
ATM	28 (4.5%)
BRCA2	18 (2.9%)
SMARCA4	10 (1.6%)
BAP1	8 (1.3%)
BRCA1	8 (1.3%)
BRIP1	6 (1.0%)
PALB2	5 (0.8%)
CHEK2	4 (0.6%)
FANCA	4 (0.6%)
FANCC	3 (0.5%)
RAD50	3 (0.5%)
STAG2	2 (0.3%)
BARD1	1 (0.2%)
CHEK1	1 (0.2%)
FANCG	1 (0.2%)

- Know Your Tumor® (KYT) Dataset
  - 16.5% HR-DDR
- Caris Database Review
  - 16.9% HR-DDR

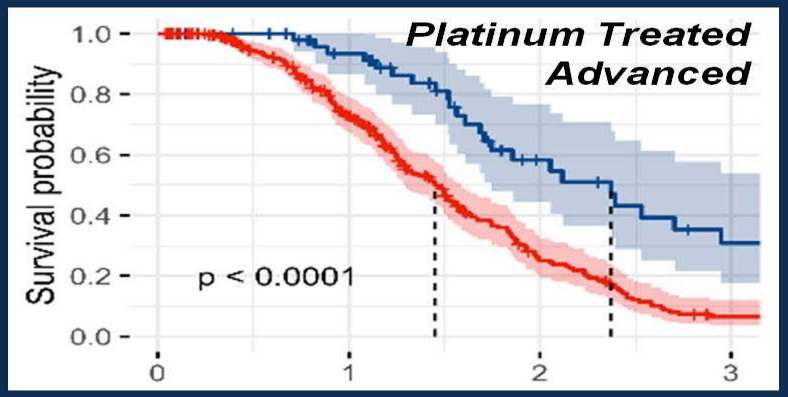
Pishvaian and Brody, Oncology (Williston Park). 2017
Pishvaian, et al, Clinical Cancer Research, 2018
Heeke, et al, JCO Precision Oncology, 2018
Aguirre, et al, Cancer Discovery, 2018
Witkiewicz, et al, Nat Commun, 2015
Lowery, et al, Clinical Cancer Research, 2017
Waddell, et al, Nature, 2015
Bailey, et al, Nature, 2016
Biankin, et al, Nature, 2012
Collisson, et al, Nat Med, 2011

Pancreas	Total N = 833
OVERALL HR-DDR	16.9%
95% CI	(14.4~19.6)
ATM	3.60%
BRCA2	3.33%
BRCA1	1.41%
PALB2	1.20%
CHEK2	0.60%
BAP1	0.48%
BRIP1	0.48%
NBN	0.12%
WRN	0.12%
ATRX	0%
BLM	0%
FANCC	0%
MRE11A	0%
RAD50	0%
ARID1A	5.54%

HR-DDR Deficiencies Predict OS Improvement in Platinum-Treated Pancreatic Adenocarcinoma



HR-DDR Status	n	mOS
Mutated	49	4.35y
Proficient	220	3.0y



HR-DDR Status	n	mOS
Mutated	54	2.37y
Proficient	258	1.45y

Olaparib as maintenance treatment following first-line platinum-based chemotherapy in patients with a germline BRCA mutation and metastatic pancreatic cancer: Phase III POLO trial

Hedy L Kindler,[1] Pascal Hammel,[2] Michele Reni,[3] Eric Van Cutsem,[4] Teresa Macarulla,[5] Michael J Hall,[6] Joon Oh Park,[7] Daniel Hochhauser,[8] Dirk Arnold,[9] Do-Youn Oh,[10] Anke Reinacher-Schick,[11] Giampaolo Tortora,[12] Hana Algül,[13] Eileen M O'Reilly,[14] David McGuinness,[15] Karen Y Cui,[16] Katia Schlienger,[17] Gershon Y Locker,[16] Talia Golan[18]

[1]The University of Chicago, Chicago, IL, USA; [2]Hôpital Beaujon (AP-HP), Clichy and University Paris VII, Paris, France; [3]IRCCS Ospedale, San Raffaele Scientific Institute, Milan, Italy; [4]University Hospitals Gasthuisberg and KU Leuven, Leuven, Belgium; [5]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [6]Fox Chase Cancer Center, Philadelphia, PA, USA; [7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [8]University College London Cancer Institute, London, UK; [9]Asklepios Tumorzentrum Hamburg AK Altona, Hamburg, Germany; [10]Seoul National University Hospital, Seoul, South Korea; [11]St Josef-Hospital, Ruhr University Bochum, Bochum, Germany; [12]Azienda Ospedaliera Universitaria Integrata Verona, Verona and Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy; [13]Klinikum Rechts der Isar, Department of Internal Medicine II, Technische Universität München, Munich, Germany; [14]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [15]AstraZeneca, Cambridge, UK; [16]AstraZeneca, Gaithersburg, MD, USA; [17]Merck & Co, Inc, Kenilworth, NJ, USA; [18]The Oncology Institute, Sheba Medical Center at Tel-Hashomer, Tel Aviv University, Tel Aviv, Israel

ClinicalTrials.gov identifier: NCT02184195. This study was sponsored by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA (MSD)

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Hedy L Kindler

Presented By Hedy Kindler at 2019 ASCO Annual Meeting

Study design

Key eligibility criteria

Metastatic pancreatic cancer

Deleterious or suspected deleterious germline *BRCA1* or *BRCA2* mutation

≥16 weeks first-line platinum-based chemotherapy with no limit to duration, without progression (CR, PR or SD)*

Randomized 3:2

No stratification factors

Olaparib tablets 300 mg bid

or

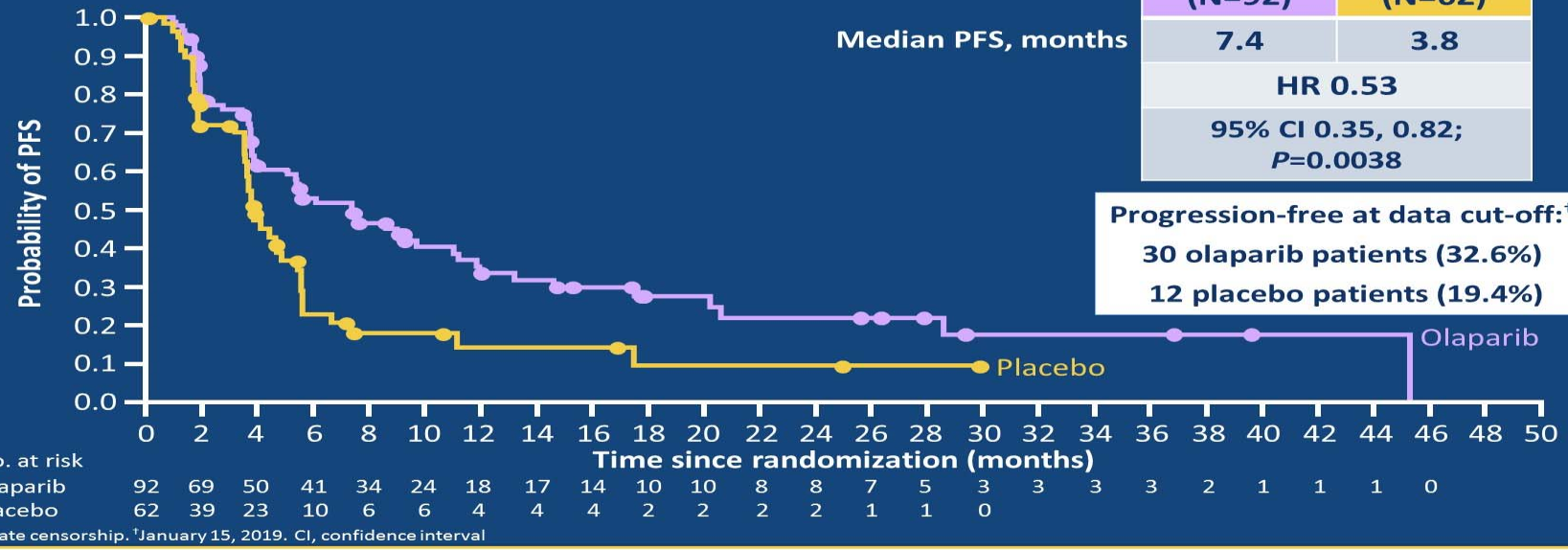
Placebo

Until investigator-assessed disease progression or unacceptable toxicity

38% of gBRCAm patients had disease progression, were ineligible, or declined randomization

*There was no maximum limit to the duration of first-line chemotherapy. bid, twice daily; CR, complete response; PR, partial response; SD, stable disease

Primary endpoint: PFS by blinded independent central review*



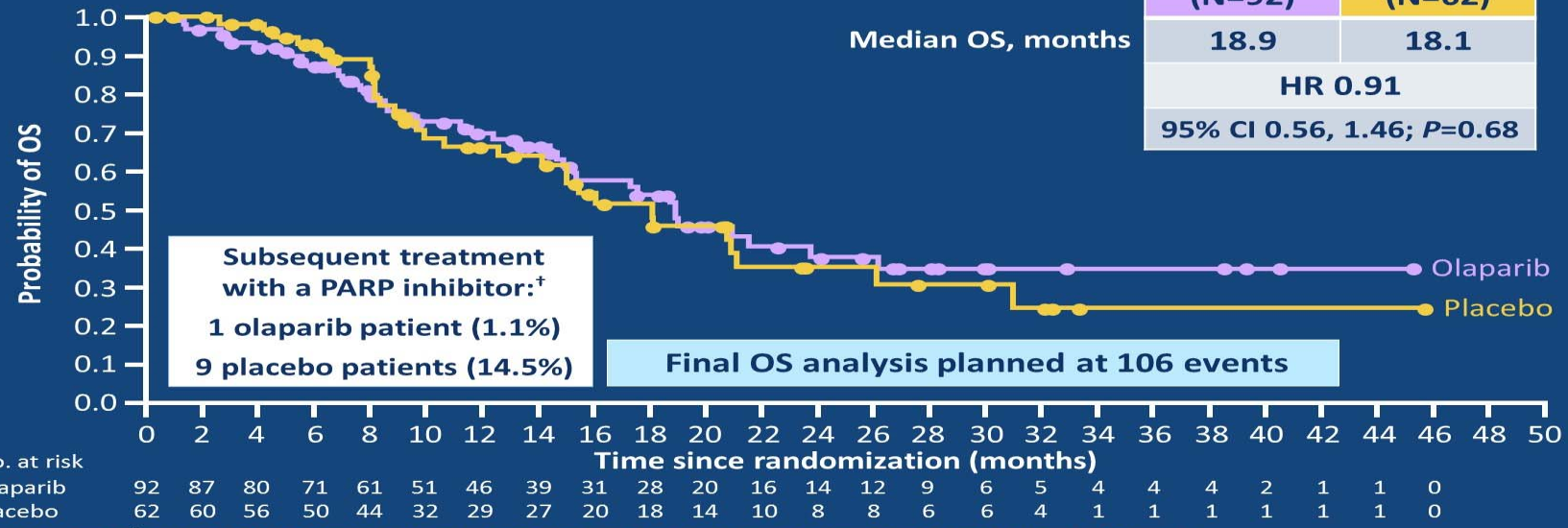
Median PFS, months	Olaparib (N=92)	Placebo (N=62)
	7.4	3.8
HR 0.53		
95% CI 0.35, 0.82; *P*=0.0038		

Progression-free at data cut-off:†
30 olaparib patients (32.6%)
12 placebo patients (19.4%)

No. at risk																							
Olaparib	92	69	50	41	34	24	18	17	14	10	10	8	8	7	5	3	3	3	3	2	1	1	1	0
Placebo	62	39	23	10	6	6	4	4	4	2	2	2	2	1	1	0								

*Dots indicate censorship. †January 15, 2019. CI, confidence interval

OS: interim analysis, 46% maturity*



	Olaparib (N=92)	Placebo (N=62)
Median OS, months	18.9	18.1
HR 0.91		
95% CI 0.56, 1.46; *P*=0.68		

No. at risk																								
Olaparib	92	87	80	71	61	51	46	39	31	28	20	16	14	12	9	6	5	4	4	4	2	1	1	0
Placebo	62	60	56	50	44	32	29	27	20	18	14	10	8	8	6	6	4	1	1	1	1	1	1	0

*Dots indicate censorship. †Crossover to olaparib was not permitted during this study; subsequent therapies were given at the investigators' discretion

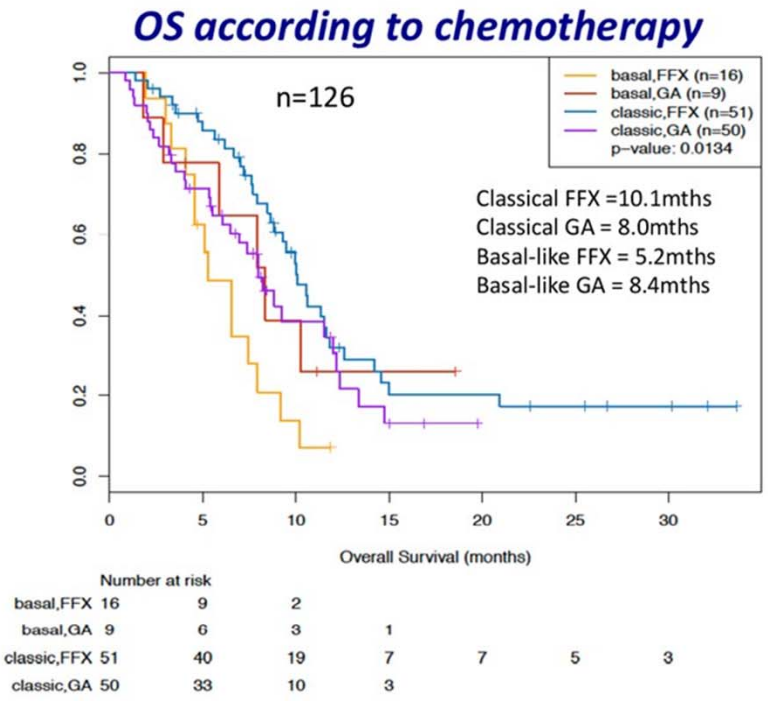
Only Germline Mutations?

- Binder et al, AACR 2019
- Germline or somatic BRCA1/2 or PALB2 mutations
- 4 months of platinum based chemotherapy→ rucaparib maintenance
- ~50% accrual: ORR 36.7%, median PFS 9.1 months

Genotype vs. Phenotype

- COMPASS study (O'Kane ASCO GI 2019)
- Prospective RNAseq/WGS
- N=157, 95% success rate
- Basal: chemoresistance
- Basal vs. Classical: median OS 6.6 vs 8.5 mo (HR 0.53)

OS by treatment and subtype



Genomic Profiling: Actionable variants

- ~40% potentially actionable

		Targeted Rx used
KRAS WT N=12, 8%	• MAPK- BRAF in frame deletion n=3, BRAF V600E n=1 • FGFR1 amplification n=1 • NTRK3-EML4 fusion n=1	BRAFi+Meki n= 1 FGFRi planned n=1
gBRCA/HRD N=9, 6%	• N=9: 7 germline BRCA, 1 biallellic somatic BRCA-2, 1 somatic biallellic RAD51C • (2 known germline BRCA mutations had no HRD signature in WGS (and poor platinum response)	Platinum switch n=3 PARPi n= 2 Novel HRD agent n=1
Others n=38 25% (co-occurring KRAS)	• Activating mutations :PIK3CA, ERBB3, ERBB4, • Inactivating mutations in STK11, PTEN, • Amplifications in HER2, CDK4/6, FGF3, FGF4, FGF19, MYC, novel ABL fusion • (1 germline MSH6 with no evidence MMRd)	Palbociclib n=2 FAKi/Meki n=3 Imatinib n =1 Plk4i I n= 1

Presented By Grainne O'Kane at 2019 Gastrointestinal Cancer Symposium

Pancreatic Adenocarcinoma 2019

- Localized Disease:
  - Gemcitabine/Nab Paclitaxel can be an adjuvant option for non FOLFIRINOX candidates
  - Germline testing recommended
- Advanced Disease:
  - Germline mutation testing recommended
  - Somatic mutation testing recommended for patients deemed eligible for systemic therapy
  - Pathogenic gBRCA1/2 mutation carriers: Platinum-based therapy followed by PARPi maintenance another treatment option

Immunotherapy and Targeted Therapy

HEPATOBILIARY CANCER

Results of KEYNOTE-240: Phase 3 Study of Pembrolizumab vs Best Supportive Care for Second-Line Therapy in Advanced Hepatocellular Carcinoma

Richard S. Finn,[1] Baek-Yeol Ryoo,[2] Philippe Merle,[3] Masatoshi Kudo,[4] Mohamed Bouattour,[5] Ho-Yeong Lim,[6] Valeriy Breder,[7] Julien Edeline,[8] Yee Chao,[9] Sadahisa Ogasawara,[10] Thomas Yau,[11] Marcelo Garrido,[12] Stephen L. Chan,[13] Jennifer Knox,[14] Bruno Daniele,[15] Scot W. Ebbinghaus,[16] Erluo Chen,[16] Abby B. Siegel,[16] Andrew X. Zhu,[17] Ann-Lii Cheng,[18] for the KEYNOTE-240 Investigators

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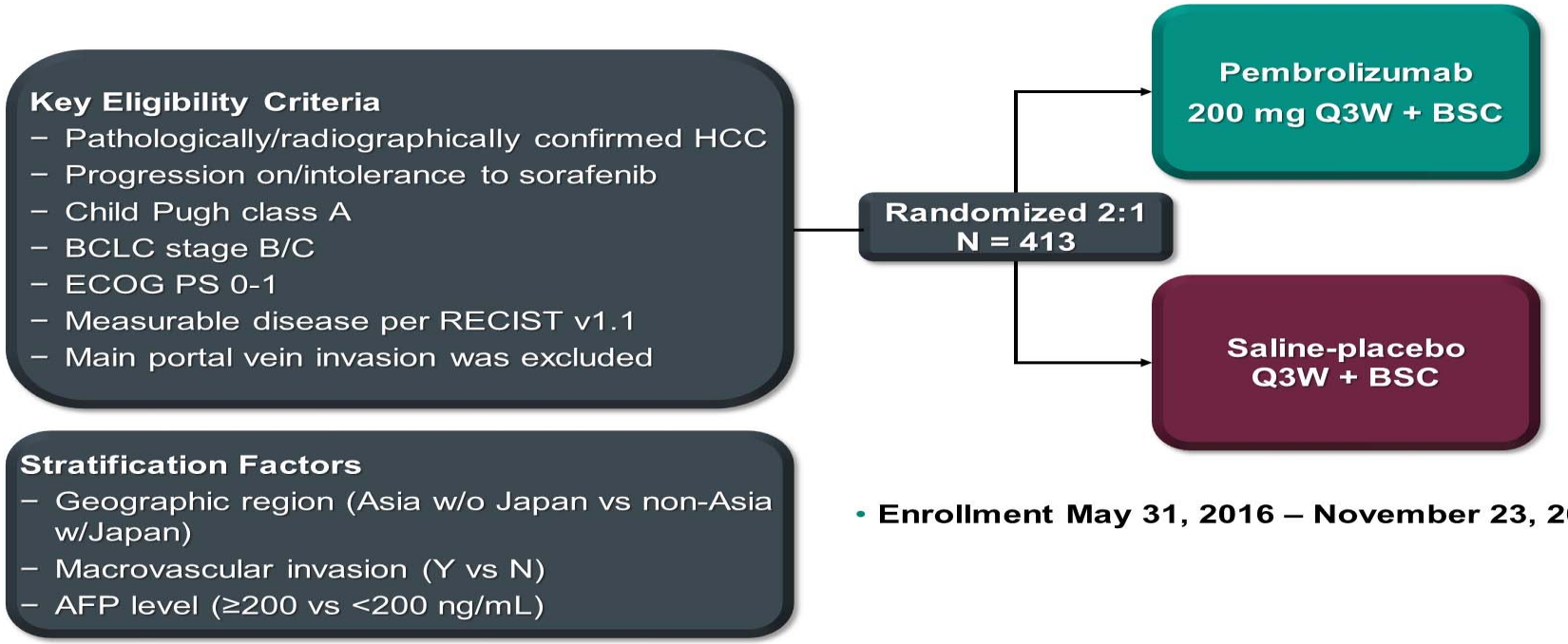
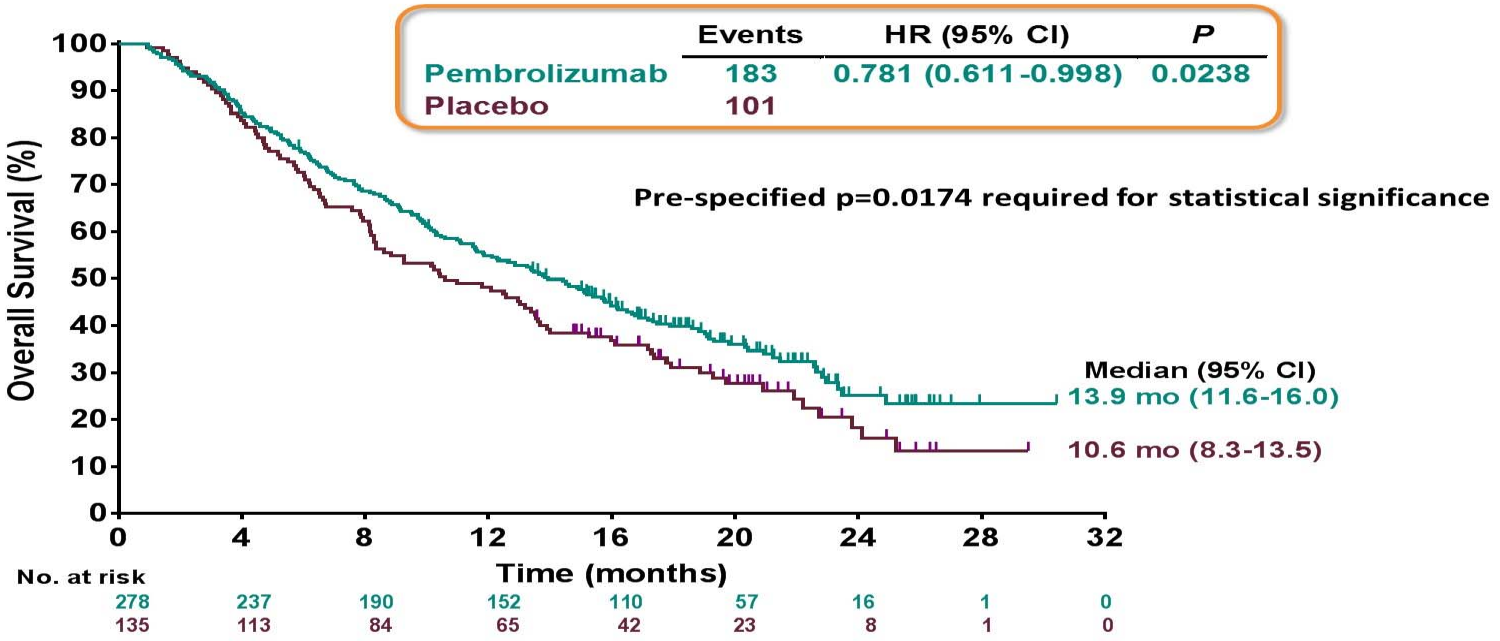
Presented By Richard Finn at 2019 ASCO Annual Meeting

KEYNOTE-240 Study Design



- **Enrollment May 31, 2016 – November 23, 2017**

Overall Survival



Data Cutoff: Jan 2, 2019.

First-line Checkpoint Inhibitors?

Bristol-Myers Squibb

Press Release

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Bristol-Myers Squibb Announces Results from CheckMate -459 Study Evaluating Opdivo (nivolumab) as a First-Line Treatment for Patients with Unresectable Hepatocellular Carcinoma

CATEGORY: R&D NEWS

MONDAY, JUNE 24, 2019 6:59 AM EDT

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced topline results from CheckMate -459, a randomized Phase 3 study evaluating Opdivo (nivolumab) versus sorafenib as a first-line treatment in patients with unresectable hepatocellular carcinoma (HCC). The trial did not achieve statistical significance for its primary endpoint of overall survival (OS) per the pre-specified analysis (HR=0.85 [95% CI: 0.72-1.02]; p=0.0752). No new safety signals were observed with *Opdivo*. The full study results will be presented at an upcoming medical meeting.

Biliary Tract Cancer: 40% with targetable alterations

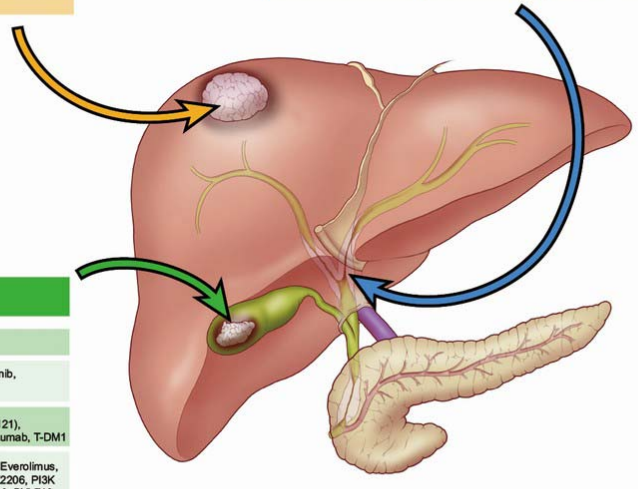
BRAF: 5%-
IHCCA mainly

IHCCA

Specific Targetable GAs	Prevalence	Targeted Therapies
FGFR2 Fusions	10% to 20%	BGJ398, Ponatinib, JNJ425756493, PRN1371, TAS-120, FGFR antibodies and FGFR trap molecules
IDH1/2	22% to 28%	AG-120, AG-881
BAP1	15% to 25%	Histone Deacetylase (HDAC) inhibitors like vorinostat and panobinostat

EHCCA

Specific Targetable GAs	Prevalence	Targeted Therapies
HER2/neu (mutation)	11% to 20%	Tyrosine Kinase Inhibitors like afatinib, neratinib, and dacomitinib
PRKACA and *PRKACB*	9%	Protein Kinase A inhibitors under development
ARID1A	5% to 12%	Histone Deacetylase (HDAC) inhibitors like vorinostat and panobinostat



GBC

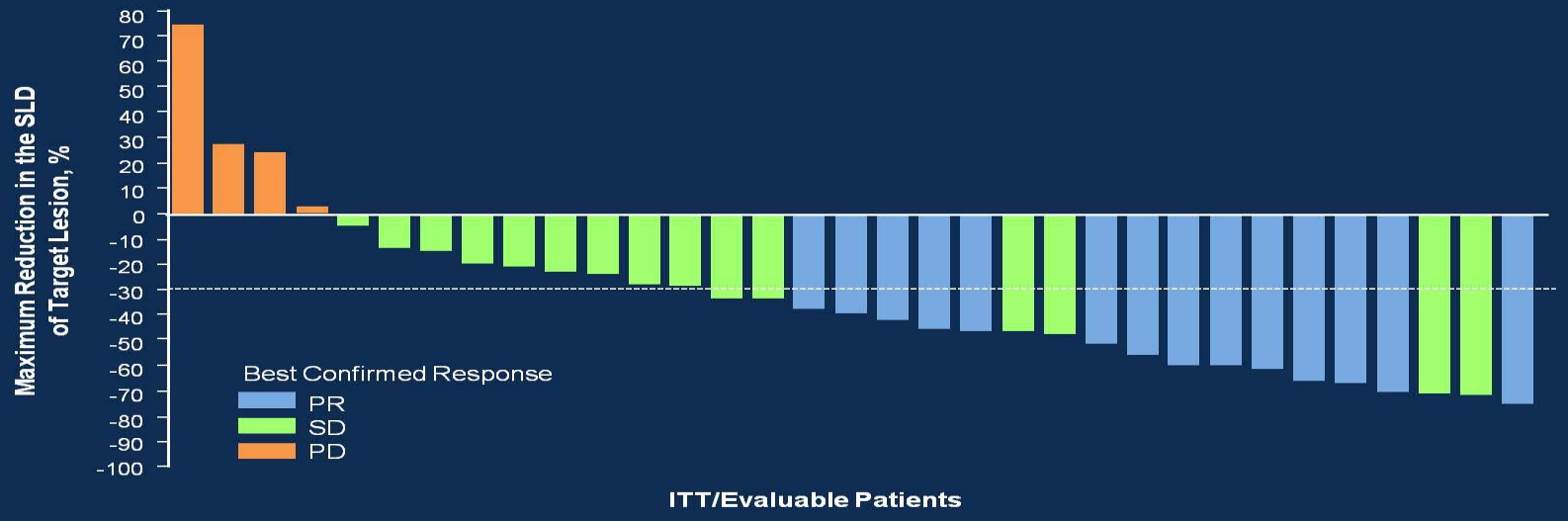
Specific Targetable GAs	Prevalence	Targeted Therapies
EGFR	4% to 13%	Erlotinib, Cetuximab
HER2/neu (amplification)	10% to 15%	Trastuzumab, Lapatinib, Pertuzumab, T-DMI
ERBB3	0% to 12%	Seribantumab (MM-121), Pertuzumab, Trastuzumab, T-DM1
PTEN	0% to 4%	mTOR inhibitors like Everolimus, AKT inhibitor like MK2206, PI3K inhibitors like BKM120, BYL719 and SF1126
PIK3CA	6% to 13%	mTOR inhibitors like Everolimus, AKT inhibitor like MK2206, PI3K inhibitors like BKM120, BYL719 and SF1126

Jain and Javle, JGO

ROAR Cholangiocarcinoma Cohort

- BRAF V600E mutation
- Dabrafenib/Trametinib
- 72% had 2 or more lines of therapy
- ORR: 41%
- PFS: 7.2 mo
- OS: 11.3 mo

Investigator-Assessed Maximum Reduction in SLD of Target Lesions



SLD, sum of the longest diameter of the target lesion.

PRESENTED AT: 2019 Gastrointestinal Cancers Symposium | #GI19

Hepatobiliary Cancers 2019

- 1st line remains lenvatinib or sorafenib
- 2nd line remains checkpoint inhibitor or regorafenib or cabozantinib or ramucirumab (AFP>400)
- All 2nd line agents tested after sorafenib
- Regorafenib not tested in sorafenib-intolerant patients.
- Cabozantinib tested in 3rd line setting (27% of patients in CELESTIAL)
- Checkpoint Inhibitors plus TKIs?
- Cholangiocarcinoma: Multiple targetable alterations, NGS should be performed in all patients eligible for systemic therapy

Escalate or De-escalate? BEACON

COLORECTAL CANCER

Should we escalate 1st-line therapy to FOLFOXIRI?

#3507 VISNU-1: FOLFOXIRI-bev vs. FOLFOX-bev in metastatic colorectal cancer and ≥3 circulating tumor cells

#3508 TRIBE-2: FOLFOXIRI-bev vs. sequential FOLFOX-bev→FOLFIRI-bev

Presented By Hanna Sanoff at 2019 ASCO Annual Meeting

#3507: VISNU-1 Design

Primary Endpoint: PFS

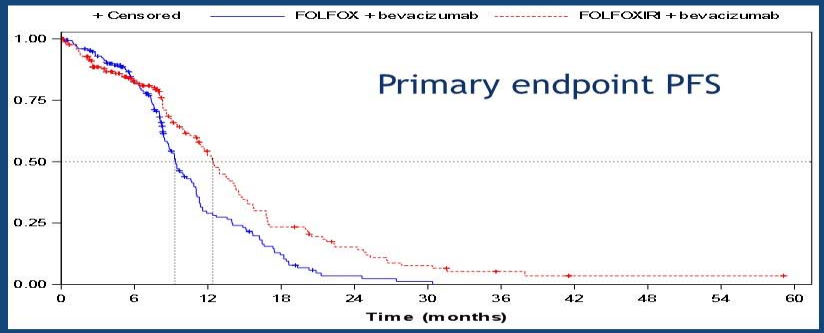
See also: Gomez A, ASCO 2018 #3536

Presented By Hanna Sanoff at 2019 ASCO Annual Meeting

VISNU-1: Key Results

- Survival shorter in pts with high CTCs
- Incremental benefit from FOLFOXIRI consistent with prior studies
- CTC is prognostic, NOT predictive of greater benefit from FOLFOXIRI

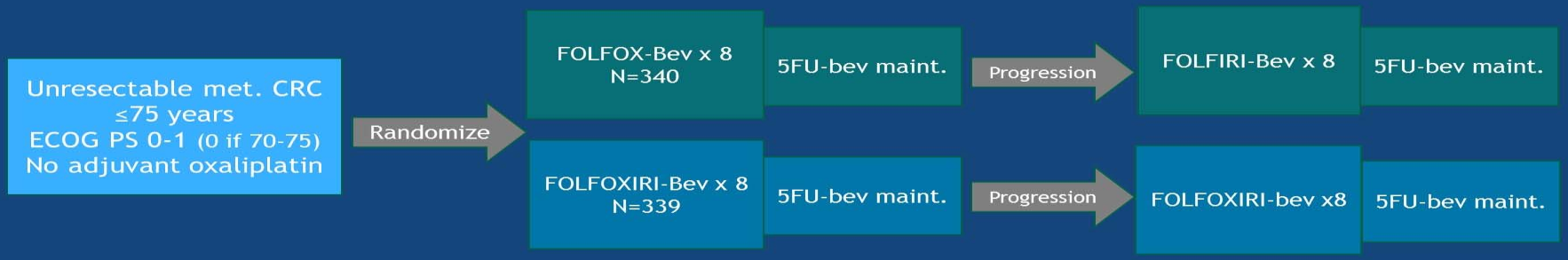
	FOLFOXIRI-bev N=172	FOLFOX-bev N=177	HR, 95% CI
PFS	12.4m	9.3m	0.64 (.49-.82)
OS	22.3m	17.6m	0.84 (.66-1.06)
RR	59%	52%	



Sastre J, et al. ASCO 2019 #3807

Presented By Hanna Sanoff at 2019 ASCO Annual Meeting

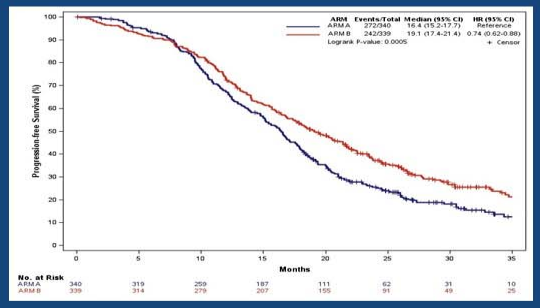
#3508 TRIBE2 Design



Primary Endpoint: PFS2
Combination chemo regimens administered for up to 8 cycles (vs TRIBE up to 12)

TRIBE2: Key Results and Take Away Points

- Good uptake of 2nd line: control FOLFIRI (88%), exp FOLFIRINOX (68%) + doublet (17%)
- Little difference in 2nd line PFS.
- Do we actually need triplet at reintroduction?



Cremolini, et al. ASCO 2019 #3808

	FOLFOXIRI-bev N=339	Sequential doublet-bev N=340	
PFS2	19.1m	17.5 m	HR 0.74 (.62-.88)
PFS1	12.0m	9.8 m	HR 0.75 (.63-.88)
OS	27.6m	22.6 m	HR 0.81 (.67-.98)
RR	62%	50% (FOLFOX-bev)	
2nd line RR	19%	12%	
2nd line PFS	6.2 m	5.6 m	HR .87 (.73-1.04)

Limits to Generalizability of VISNU1 + TRIBE2

- Both excluded most patients over 70 years
- Both excluded patients with PS 2
- No patients treated with prior adjuvant oxaliplatin

UNIQUE TO FOLFOXIRI QUESTION:
- No benefit in adjuvantly treated patients in TRIBE (n=64), HR 1
- No adjuvantly treated patients in TRIBE2
- 15 (4%) in VISNU1

WE SHOULD NOT ASSUME FOLFOXIRI OFFERS PFS OR SURVIVAL BENEFIT IN PATIENTS TREATED WITH ADJUVANT OXALIPLATIN

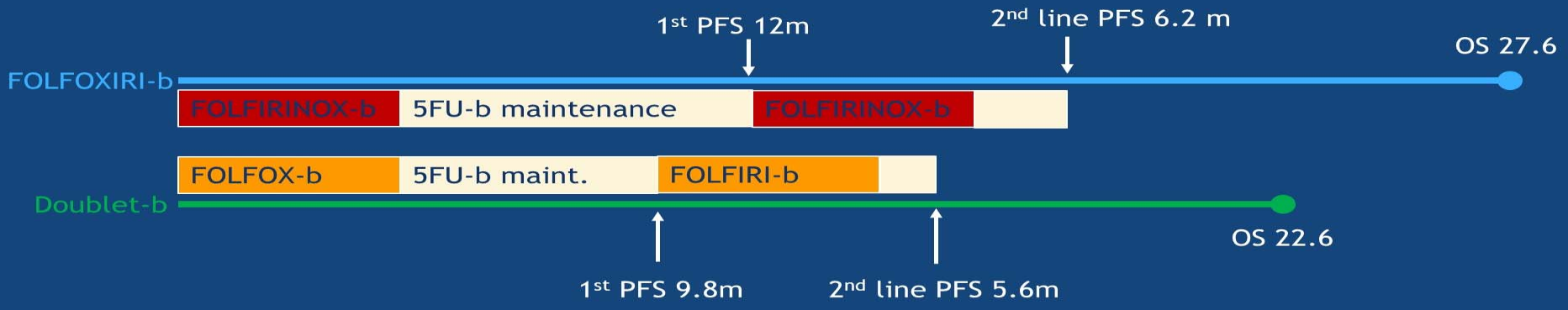
Absolute INCREASES in Grade ≥3 Toxicity

	VISNU-1 FFRI vs FOLFOX % Absolute Increase	TRIBE2 FFRI vs FOLFOX % Absolute Increase	TRIBE FFRI vs FOLFIRI % Absolute Increase
All Grade ≥ 3	15%	Nr	Nr
Grade ≥ 3 diarrhea	15%	12%	8%
Grade ≥ 3 neutropenia	10%	19%	30%
Grade ≥ 3 asthenia	9%	1%	3%
Grade ≥ 3 mucositis	5%	2%	4%
Treatment-related mortality	2 more pts	nr	2 more pts

*** We have no systematically collected patient reports (PROs) on how this affects the experience of treatment for mCRC from these trials***

Presented By Hanna Sanoff at 2019 ASCO Annual Meeting

Which TRIBE2 Arm is More Patient Centered?



FOLFOXIRI	VS	FOLFOX then FOLFIRI
Triplet time: 8 months		Doublet time: 8 months
Maintenance time: 10.2 months		Maintenance time: 7.4 months

BEACON Study

BEACON CRC:

A Randomized, 3-Arm, Phase 3 Study of Encorafenib and Cetuximab With or Without Binimetinib vs. Choice of Either Irinotecan or FOLFIRI, plus Cetuximab in *BRAF*^{V600E} Mutant Metastatic Colorectal Cancer

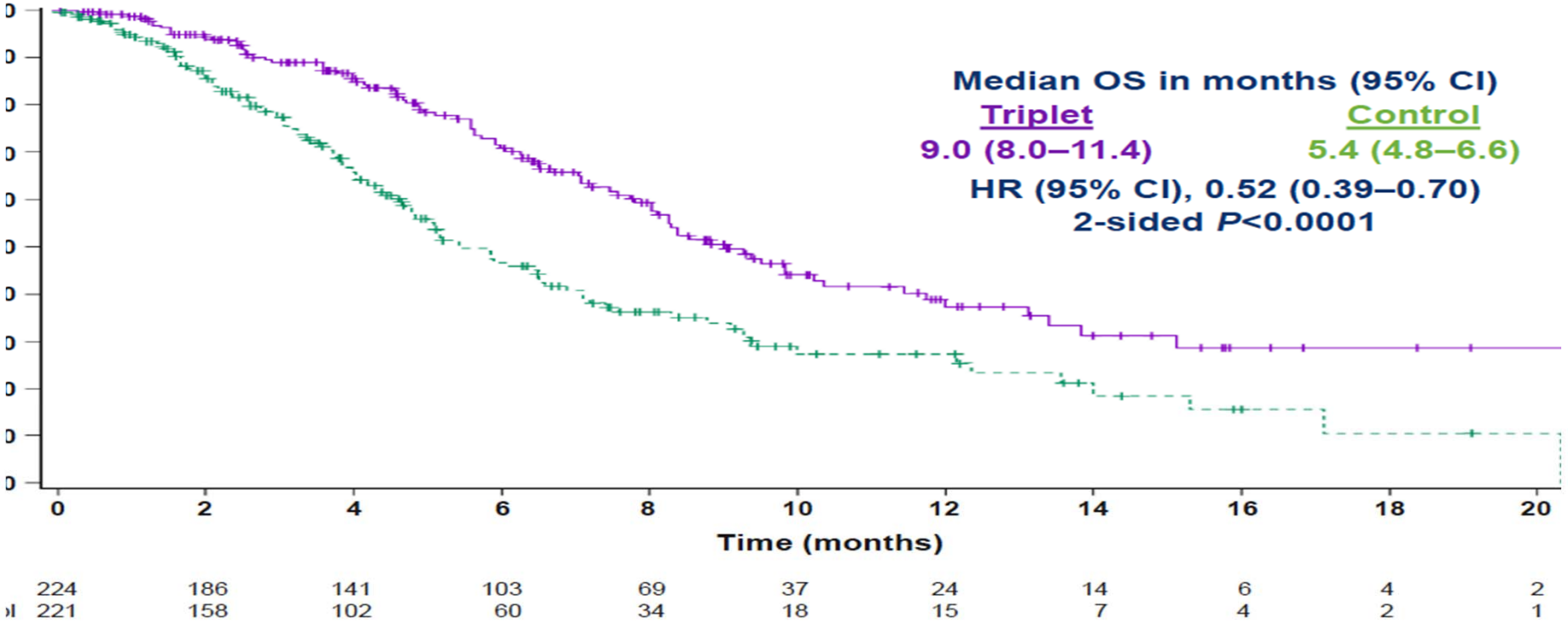
Scott Kopetz, Axel Grothey, Eric Van Cutsem, Rona Yaeger, Harpreet Wasan, Takayuki Yoshino, Jayesh Desai, Fortunato Ciardiello, Fotios Loupakis, Yong Sang Hong, Neeltje Steeghs, Tormod Kyrre Guren, Hendrik-Tobias Arkenau, Pilar Garcia-Alfonso, Ashwin Gollerkeri, Kati Maharry, Janna Christy-Bittel, Lisa Anderson, Victor Sandor, and Josep Tabernero

BEACON CRC: **B**inimetinib, **E**ncorafenib, **A**nd **C**etuximab C**O**mbi**N**ed to Treat *BRAF*-mutant **C**olo**R**ectal **C**ancer

Endpoint - Overall Survival: Triplet vs Contro

ıized patients)

ORR: 26% vs. 2%

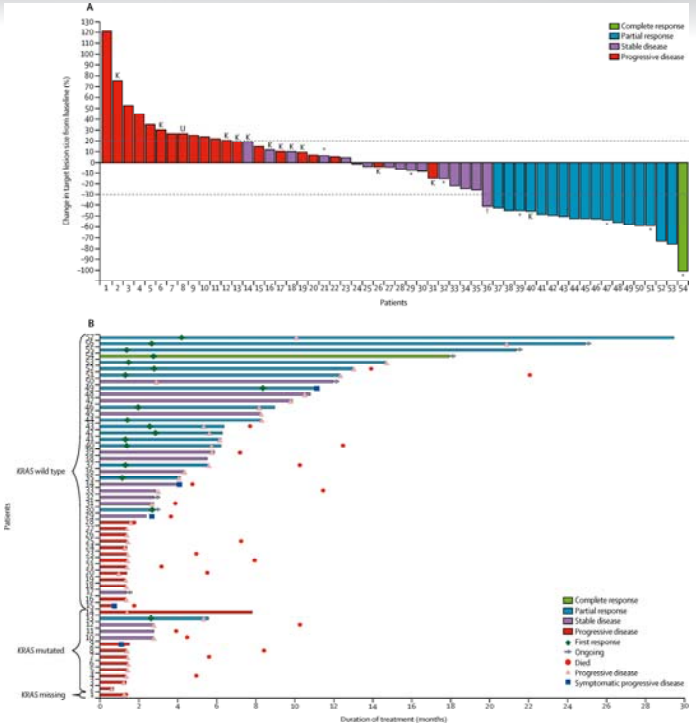


HER2+ Colorectal Cancer: MyPathway

Trastuzumab/Pertuzumab

Outcomes

	ORR %	DCR %	PFS (mo)	OS (mo)
Overall (n=57)	32	44	2.9	11.5
KRAS wt/mt	40/8	56/8	5.3/1.4	14/8.5
PI3K wt/mut	43/13	58/25	5.3/1.4	14/7.3
Prior EGFR no/yes	50/36	67/52	5.6/4.1	NE/11.5



The Lancet Oncology 2019 20, 518-530DOI: (10.1016/S1470-2045(18)30904-5)

Colorectal Cancer 2019

- Advanced Disease: Is treatment intensification desirable for all patients?
  - FOLFOXIRI: **Yes for BRAF^{V600}**. Unclear for the rest.
  - BRAF/MEK/EGFRi: **Yes for BRAF^{V600}**
  - Triple (-) Colorectal cancer (i.e. wtKRAS/NRAS/BRAF): Think HER2, ongoing studies

VEGFR Inhibition in ENETs

NEUROENDOCRINE TUMORS

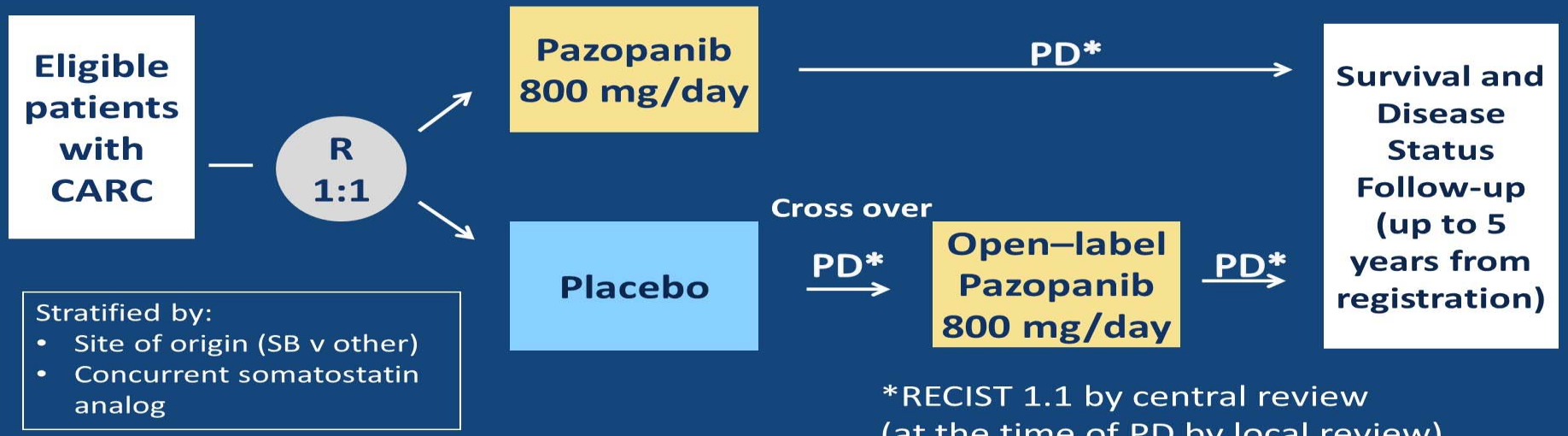
Abstract #4005: Randomized phase II trial of pazopanib versus placebo in patients with progressive carcinoid tumors (Alliance A021202)

Emily K. Bergsland[1], Michelle R. Mahoney[2], Timothy R. Asmis[3], Nathan Hall[4], Priya Kumthekar[5], Michael L. Maitland[6], Donna Niedzwiecki[7], Andrew B. Nixon[7], Eileen Mary O'Reilly[8], Lawrence Howard Schwartz[9], Jonathan R. Strosberg[10], Jeffrey A. Meyerhardt[11]

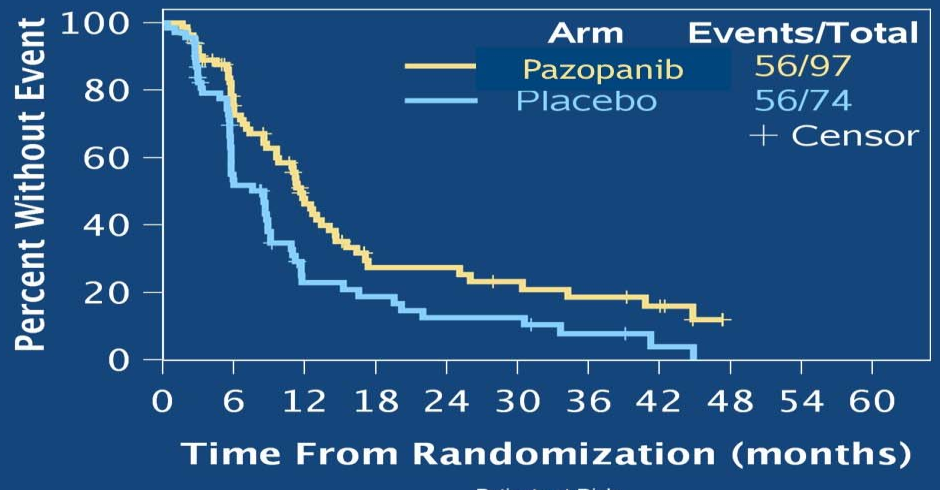
1.University of California San Francisco, San Francisco, CA; 2.Mayo Clinic, Rochester, MN; 3.Ottawa Hospital Cancer Centre, Ottawa, ON; 4.University of Pennsylvania, Philadelphia, PA; 5.Northwestern Memorial Hospital, Chicago, IL; 6.Inova Center for Personalized Health and University of Virginia, Falls Church, VA; 7. Duke University Medical Center, Durham, NC; 8. Memorial Sloan Kettering Cancer Center, New York, NY; 9.Columbia University Medical Center, New York, NY; 10.Moffitt Cancer Center, Tampa, FL; 11.Dana-Farber Cancer Institute/Partners CancerCare, Boston, MA

Presented By Emily Bergsland at 2019 ASCO Annual Meeting

A021202: Randomized phase II, double blind, placebo-controlled clinical trial



Progression Free Survival (Central Review, ITT)



	Pazopanib (N=97)	Placebo (N=74)
No. of events	56	56
12 mo. PFS, % (90% UCB*)	46.4 (54.7)	22.9 (31.4)
Median PFS, mo. (90% UCB)	**11.6 (13.0)**	**8.5 (8.9)**
HR (90% UCB)	**0.53 (0.69)**	**REF**
Stratified Log-Rank P-value = 0.0005		
Adj. HR** (90% UCB)	0.57 (0.74)	REF
Adjusted Log-Rank P-value = 0.0020		

**Gender, functional tumor, age, and stratification factors (concurrent SSA, site of primary)

*UCB=Upper Confidence Bound

Question 1

55 yo man with metastatic squamous carcinoma of esophagus. PS=1, progression after cisplatin/5FU. CPS=5, MSS. Options for second line?

1. Pembrolizumab
2. Paclitaxel
3. Paclitaxel/Ramucirumab
4. Irinotecan
5. 2 and 4

Question 2

55 yo man with metastatic adenocarcinoma of GEJ, HER2 –ve, PS=1, progression after FOLFOX and paclitaxel/ramucirumab. CPS=5, MSS. Options for third line?

1. Pembrolizumab
2. Irinotecan
3. Trifluridine/Tipiracil
4. Epirubicin
5. 1, 2 and 3

Question 3

55 yo man with metastatic pancreas adenocarcinoma, PS=0. FFX for 4 months with partial response. Germline testing: BRCA1 VUS; NGS: MSI-S, KRASmt, p53mt, CDKN2Amt. Next steps?

1. Continue FFX
2. 5FU maintenance
3. Olaparib maintenance
4. Palbocyclib
5. 1 and 2

Question 4

55 yo woman with metastatic HCC, HepC related. Received sorafenib for 6 months with poor tolerance (fatigue and hand-foot syndrome requiring multiple dose reductions and treatment holidays). Finally progresses, maintaining PS=1 and CP score=A(6). AFP>1500, Appropriate options for her?

1. Nivolumab
2. Pembrolizumab
3. Regorafenib
4. Ramucirumab
5. 1, 2 and 4

Question 5

55 yo woman with metastatic colorectal cancer, KRASwt/NRASwt/BRAFwt/HER2 amplified by FISH, PS=1, Progressed on fluroropyrimidine, oxaliplatin, irinotecan, bevacizumab. Appropriate options for her?

1. Irinotecan/Cetuximab
2. Referral for dual HER2 study
3. Regorafenib
4. Trifluridine/Tipiracil
5. 1 and 2

Questions

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